# Attachment 1

## Diabetes *mellitus* and market analysis

Diabetes *mellitus* (DM) is defined as a group of metabolic diseases characterized by increased blood glucose levels or hyperglycaemia, essentially caused by a deficient insulin action on target tissues. DM typical symptoms include polyuria, polydipsia, weight loss, polyphagia and blurred vision. Growth deficiencies and lowered immunization to certain infections are also included as DM manifestations, and uncontrolled hyperglycaemia is also related to diabetic ketoacidosis or nonketotic hyperosmolar syndrome.(1) Long-term DM is a leading cause of serious microvascular and macrovascular complications. Microvascular complications are due to small blood vessels damage and include retinopathy (leading to blindness), nephropathy (leading to renal failure) and neuropathy (leading to impotence and diabetic foot disorders, which may lead to amputation). Macrovascular complications are due to larger blood vessels damage and include cardiovascular diseases, such as heart failure, strokes and venous insufficiency or peripheral artery disease of the legs.(2)

DM exhibits two different etiopathogenetic categories: DM type 1, an autoimmune disease which represents 5-10% of total diagnosed diabetic population, and DM type 2 or non-insulin-dependent diabetes mellitus (NIDDM), which represents the remaining 90-95% diabetic population.(1) The present work further focuses on NIDDM.

NIDDM is caused either by a mechanism of insulin resistance or by a relative impairment in the insulin secretion process.(3,4) Insulin resistance or defective insulin-stimulated glucose transport activity is reported to be caused by an increase in intra-mitochondrial lipid metabolites concentration (such as fatty-acyl-CoAs and diacylglycerol), which activate a serine/threonine kinase cascade, thus leading to defects in insulin signalling through serine/threonine phosphorylation of insulin receptor substrate. As a result, insulin cannot bind correctly to its cell-membrane receptor, therefor causing the cell's incapacity to absorb and process glucose and leading to high blood glucose levels. However, plasma glucose signalling remains functioning and more insulin is produced and secreted by the pancreatic-β-cells, further contributing to high insulin blood levels and consequently insulin resistance.(5,6)

Insulin resistance and secretion impairment of this hormone have been linked to a variety of factors such as heredity, environmental factors, unhealthy eating habits, sedentary lifestyle and stress. Installed worldwide consumerism and urban culture encouraging the prevalence of those epidemiologic factors makes NIDDM one of the biggest epidemic diseases of the twenty-first century.(7) World Health Organization (WHO) recently published "Global Report on Diabetes" estimates that DM prevalence has approximately doubled since 1980, advancing in adult population from 4.7% (108 million people) to 8.5% (422 million people) of global population in 2014.(8) International Diabetes Federation (IDF) atlas poster summarizes DM global numbers and reveals that this silent disease (one in two adults with DM is undiagnosed), although not choosing gender (215.2 million men *vs.* 199.5 million women, in 2015), definitely has a greater prevalence in urban areas compared to the rural environment (269.7 million *vs.* 145.1 million people, respectively), thus confirming the implication of the epidemiologic factors in the incidence and prevalence of the disease. This document also reports that, in 2015, 12% of global health expenditure ($673 billion United States Dollars (USD)) was spent on diabetes.(9)

For the pharmaceutical industry, in 2015, health expenditure in DM returned in an estimated revenue of $75.1 billion USD, representing approximately 7,9% of global pharmaceutical market revenues ($954.1 billion USD).(10–12) The broad diabetes therapeutic market is mainly segmented in two different groups: products used in diagnosis and monitoring (including syringes and other insulin delivery devices, continuous blood glucose meters, test

strips, lancets and glucose meters) and products used in treatment (including insulin and anti-diabetic drugs). Figure 1 presents the world diabetes market forecast by segment between 2009 and 2018, highlighting both segmentation by revenue values (in $millions USD) and segmentation by total diabetes market percentage.(13) Concerning only the products used in diabetes treatment segment, the pharmaceutical industry raised in 2015 an estimated revenue of $43-48 billion USD, thus placing antidiabetic drugs in the second place rating of leading therapy classes by expenditure and covering approximately 4.8% of the global pharmaceutical market revenues.(13–15)

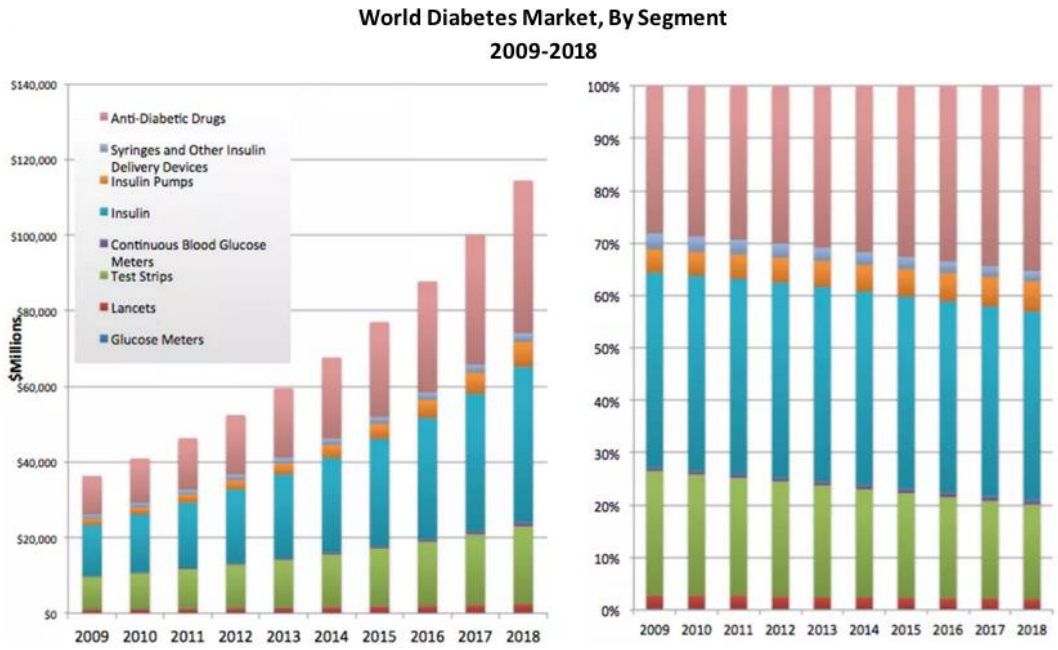


Figure 1 – World diabetes market by segment between 2009 and 2018 (data from 2011, forecast from 2012 to 2018): (left graph) diabetes market segments and total diabetes market revenue in $million USD, (right graph) diabetes market segments by total diabetes market percentage. (Adapted from "Diabetes Management: Products, Technologies, Markets and Opportunities Worldwide 2009-2018", by MedMarket Diligence, LLC, Report #D510).(13)

According to the IDF “Global Guideline for Type 2 Diabetes” and to the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) “Comprehensive Diabetes Management Algorithm”, NIDDM treatment is primarily focused on lifestyle modifications (including diet and physical activity, weight management, foot care and sick day management), being pharmacologic treatment required only when glycaemia control management (fasting plasma glucose > 100 mg/dL blood, 2-hour post-meal glucose > 140 mg/dL blood) cannot be achieved by that route. Because diabetes includes one of the several heart disease risk factors, management of the disease must involve frequent physiological evaluation of not only blood glucose levels (fasting and post-meal) but also of cholesterol, triglycerides and blood pressure. Table 1 summarizes the recommended goals for each physiological parameter.(16–19)

Table 1 – Recommended physiological parameters goals for diabetic patients according to AACE/ACE Guidelines(17,18)

| MEASURES | RECOMMENDED GOAL |
|---|---|
| **Blood Glucose Levels** | |
| Fasting blood glucose | 70-130 mg/dL |
| Post-meal (2 hour) blood glucose | ≤180 mg/dL |
| Haemoglobin A1c (HbA1c) | ≤7.0% |
| **Cholesterol** | |
| Total cholesterol | ≤200 mg/dL |
| LDL-cholesterol | ≤100 mg/dL |
| HDL-cholesterol | ≥40 mg/dL for men, ≥50 mg/dL for women |
| **Triglycerides** | ≤150 mg/dL |
| **Blood Pressure** | ≤130/80 mmHg |

According to the diabetes management goals for NIDDM, pharmacological options for blood glucose control can be classified into four main lines of action, including in the first two stages only oral antidiabetic drugs and progressing for associations of those drugs with different types of insulin (see Figure 2).(16–19)

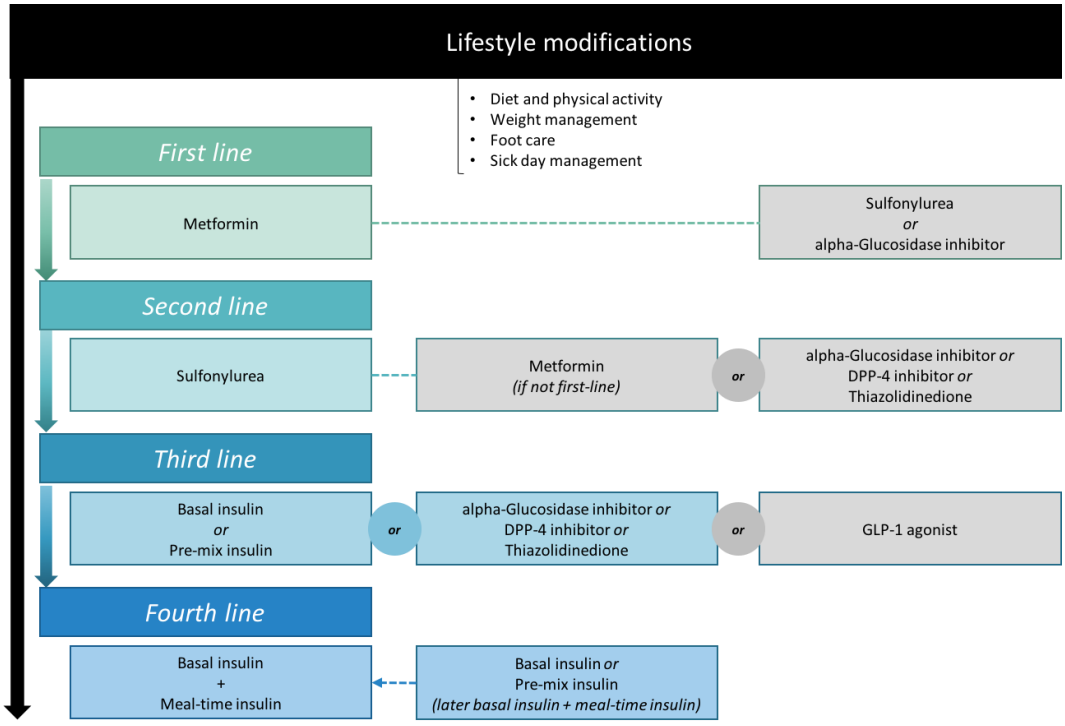


Figure 2 – Simplified representation of the NIDDM therapeutic management algorithm according to IDF and AACE/ACE guidelines

Focusing on the non-insulin segment, the main drug classes prescribed as standard of care (SOC) are biguanides (metformin), sulfonylureas (SU) (glipizide, glibenclamide, gliclazide, glimepiride) and α-glucosidase inhibitors (acarbose, voglibose, miglitol). Add-on therapies include incretin-based therapies composed of glucagon-like peptide-1 (GLP-1) analogues or receptor agonists, dipeptidyl-peptidase-4 (DPP-4) inhibitors, thiazolidinediones (TZD), and newest classes including sodium-glucose co-transporter 2 (SGLT2) inhibitors and others (e.g.:

bromocriptine).(19,20) Each therapeutic class meets different advantages and disadvantages (as displayed on Table 2), which are a result of their diverging line of action and consequent effects on the goal physiological parameters (as presented on Table 3). The divergences between the existing antidiabetic therapeutic classes justify their use in different stages of the disease and its administration choice must be individually aligned with each patient case.

Table 2 – Summarized advantages and disadvantages of antidiabetic drugs by therapeutic class

| ADVANTAGES | DISADVANTAGES |
|---|---|
| **SU** | |
| • Fast onset of action;<br>• No changes on blood pressure;<br>• No changes on LDL-cholesterol;<br>• Convenient dosing;<br>• Low cost (generics availability). | • Weight gain;<br>• Increased risk of hypoglycaemia (mainly glibenclamide). |
| **Biguanides** | |
| • Low risk of hypoglycaemia;<br>• No weight changes;<br>• Decrease on LDL-cholesterol;<br>• Decrease on triglycerides;<br>• No changes on blood pressure. | • Increased risk of gastrointestinal side effects (nausea, diarrhea);<br>• Contraindicated to diabetic patients with moderate-severe kidney disease or heart failure;<br>• Less convenient dosing. |
| **α-Glucosidase Inhibitors** | |
| • Lower risk of hypoglycaemia (compared to SU);<br>• No weight changes;<br>• Decrease on triglycerides;<br>• No changes on cholesterol. | • Less effective on HbA1c reduction;<br>• Increased risk of gastrointestinal side effects (nausea, diarrhea);<br>• Inconvenient dosing;<br>• High cost (generics not available at the moment). |
| **GLP-1 Analogues or Receptor Agonists** | |
| • Significant reduction on HbA1c;<br>• Favourable effect on weight;<br>• Minimal risk of hypoglycaemia. | • Increased risk of gastrointestinal and injection-site side effects;<br>• Need for subcutaneous administration;<br>• High cost (generics not available at the moment). |
| **GPP-4 Inhibitors** | |
| • Low risk of hypoglycaemia when combined with metformin (compared to SU);<br>• Few known side effects;<br>• Convenient dosing. | • Associated with pancreatitis;<br>• Less effective on HbA1c reduction;<br>• Only valuable as add-on drugs;<br>• Less data on potential side effects (recent drugs);<br>• High cost (generics not available at the moment). |
| **SGLT2 Inhibitors** | |
| • High effectiveness on lowering HbA1c and both fasting and post-meal glucose;<br>• Low risk of hypoglycaemia;<br>• Favourable effect on weight;<br>• Decrease on triglycerides;<br>• Increase on HDL-cholesterol;<br>• Lowering effect on blood pressure. | • Several severe side effects (vulvovaginal candidiasis, mycotic infections, osmotic diuresis, hyperkalaemia);<br>• Dosing must be based on kidney function;<br>• Increase on LDL-cholesterol<br>• High cost (generics not available at the moment). |

Table 3 – Antidiabetic therapeutic classes and correspondent drugs summarized description: general line of action, average point reduction in HbA1c (percentage), average point change in blood pressure (mmHg), average absolute change in LDL-cholesterol (mg/dL), average absolute change in HDL-cholesterol (mg/dL), average absolute change in triglycerides (mg/dL), risk of hypoglycaemia (% of people), and average change in weight (kg). (Adapted from "The Oral Diabetes Drugs: Treating Type 2 Diabetes (Comparing Effectiveness, Safety and Price)", by Consumer Reports Best Buy Drugs, 2009. Copyright 2006-2016 Consumer Reports).(19)

| Therapeutic Class | Drugs | General line of action | ΔHbA1c (mean%) | ΔBlood pressure (mean mmHg) | ΔLDL-cholesterol (mean mg/dL) | ΔHDL-cholesterol (mean mg/dL) | ΔTriglycerides (mean mg/dL) | Risk of hypoglycaemia (% of people) | ΔWeight (mean kg) |
|---|---|---|---|---|---|---|---|---|---|
| **Biguanides** | Metformin | Inhibits glucose production by the liver and ↓insulin resistance | ↓0.9-1.4 | ♦ | ↓5-7 | ♦ | ↓15-25 | 0-7 | ♦ |
| **SU** | Glimepiride | ↑insulin secretion by the pancreas | ↓1.3-1.8 | ♦ | ♦ | ♦ | ↓10-20 | 10-22 | ↑2.27-4.54 |
| | Glipizide | | ↓1.3-1.8 | ♦ | ♦ | ♦ | ↓10-20 | 10-15 | ↑2.27-4.54 |
| | Glyburide/ Glibenclamide | | ↓1.3-1.8 | ♦ | ♦ | ♦ | ↓10-20 | 9-14 | ↑2.27-4.54 |
| | Gliclazide | | ↓1.3-1.8 | ♦ | ♦ | ♦ | ↓10-20 | | ↑2.27-4.54 |
| **α-Glucosidase Inhibitors** | Acarbose | Delay glucose absorption by the intestine | ↓0.6-0.9 | IE | ♦ | ♦ | ↓10-15 | 0-5 | ♦ |
| | Miglitol | | ↓0.4-0.9 | IE | IE | IE | IE | IE | IE |
| **DPP-4 Inhibitors** | Saxagliptine | Promote release of insulin by the pancreas after meal | ↓0.4-0.9 | IE | IE | IE | IE | IE | IE |
| | Sitagliptine | | ↓0.6-0.8 | IE | ♦ | ♦ | ♦ | Low | ♦ |
| **TZD** | Pioglitazone | ↓insulin resistance | ↓0.9 | ♦ | ↑8-12 | ↑5 | ↓35-45 | 0-3 | ↑2.27-4.54 |
| | Rosiglitazone | | ↓0.9 | ♦ | ↑12-15 | ↑3 | ↓10-20 | 4-11 | ↑2.27-4.54 |
| **SGLT2 Inhibitors** | Canagliflozin | ↑glucose excretion | ↓0.9 | ↓3.3-5.0 | ↑4.5 | ↑5 | ↓5.3 | Low | ↓2-3 |

Table Symbols and Acronyms:

Δ - Variation
% - Percentage
↓ - Decrease
↑ - Increase

IE – Insufficient Evidence (to reach meaningful conclusions)
♦ - No meaningful change

Market analysis reports on type 2 diabetes therapeutics show unanimous growth on the use of antidiabetic drugs but variable consumption patterns concerning the different therapeutic classes over the last decades (1990's-2010's). A 2011 analysis study performed on the Moroccan population antidiabetic drugs consumption during 1991-2005 report that the Defined Daily Dose (DDD) per thousand inhabitants per day increased from 1.37 to 4.22, being the largest consumption share in volume held by sulfonylureas (72.22%) followed by the biguanides (22.22%). This study also demonstrates a growing consumption pattern on biguanides between 2000-2005, concluded to be a result of increased disease incidence and diabetic patient number, since metformin is suggested as first line therapy by the international guidelines.(21) Similarly, an INFARMED antidiabetics consumption study between 2000-2013 reports an overall growth of 94% on the oral antidiabetic drugs use with variable consumption pattern by therapeutic class showed in terms of DDD per thousand inhabitants per day. Figure 3 illustrates the antidiabetic therapeutic class utilization evolution during the studied period, highlighting a consistent increase in biguanides, DDP-4 inhibitors and recent biguanides-DDP-4 inhibitors association drugs consumption in detriment of SU, which utilization pattern shows a decrease between 2003 and 2010 and stabilizing since that and the last evaluated year. In 2013, antidiabetic drug combinations represent more than 35% of the total antidiabetic drugs consumption versus the approximate 30% share for each biguanides and SU.(22) Comprehensiveness of not only diabetes increased incidence but also value of convenience in taking one pill embedding two different active pharmaceutical principles (APIs) for late-diagnosed patients and for first-line therapeutic failure cases can here be discussed.

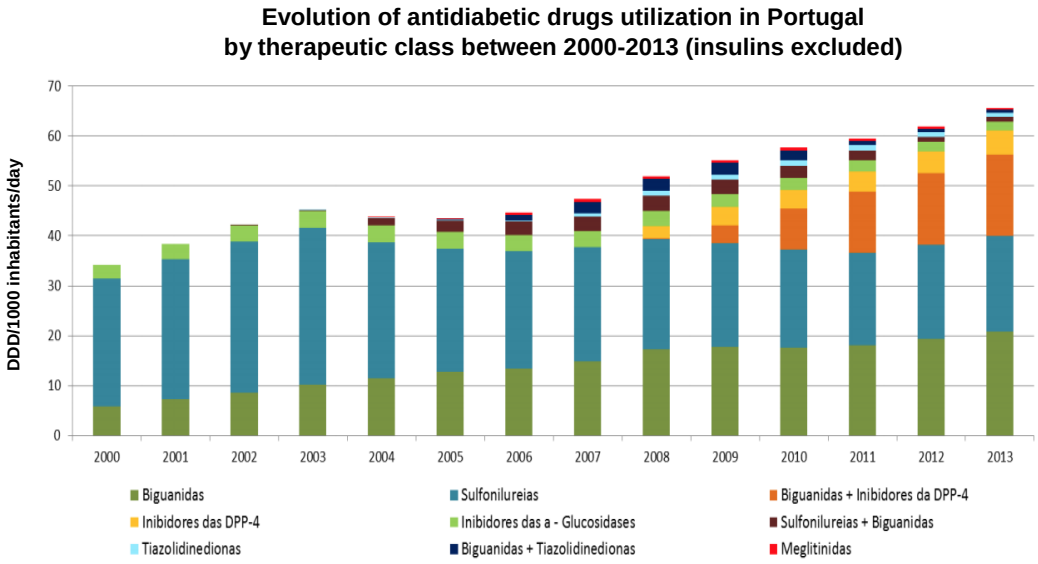


Figure 3 – Graphic representation of utilization evolution of antidiabetic drugs in Portugal by therapeutic class between 2000-2013 (insulins excluded). (Adapted from "Consumo de antidiabéticos 2000-2013", by C. Furtado and R. Oliveira, 2014, p. 5. Copyright by INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde I.P.)(22)

Considering a broader point of view and assuming United States data as representative of the global market (58% of global antidiabetic market)(23), an American Diabetes Association study on the use of antidiabetic drugs in the United States of America between 2003 and 2012 confirms similar observations, showing an increase in the total number of noninsulin antidiabetic drugs prescription by 36.2%. During the analysed period, use of biguanides (metformin) increased by 97% and the use of SU remained constant in terms of

prescription volume, but decreased from 36.3% (2003) to 26.7% (2012) in share among noninsulin antidiabetic drug prescriptions (Figure 4). Also, antidiabetic drug combination (AD/AD combination) prescriptions revealed an increase between 2007 and 2012, but divergently from the Portuguese reality, they represented only 7% of the market share in the last year of analysis.(24)

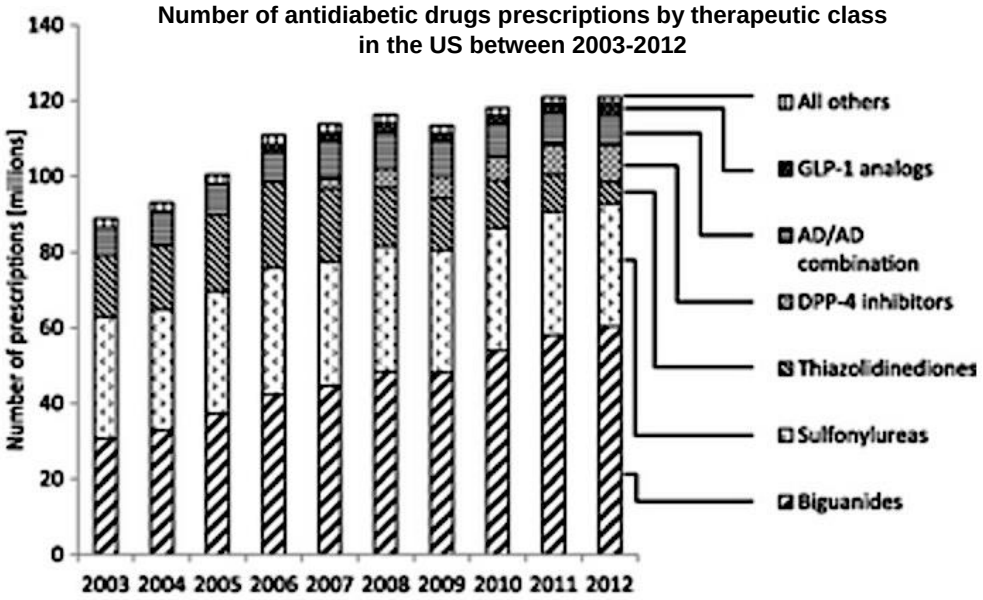


Figure 4 – Graphic representation of antidiabetic drugs prescription by therapeutic class in the US between 2003-2012. (Adapted from "Use of Antidiabetic Drugs in the U.S., 2003-2012", by C. Hampp et al., 2014, *Diabetes Care*, 37(5), p. 1367-1374. Copyright American Diabetes Association)(24)

Regarding antidiabetic expenditure by therapeutic class, the same referred INFARMED study displays national increased burden since 2008 with DDP-4 inhibitors and biguanides-DDP-4 inhibitors association market introduction (Figure 5).(22)

In this scope, availability of low-cost generic drugs versus patent protection of newly introduced drugs plays an important role when judging antidiabetic market evolution. Comparative analysis of both consumption and expenditure evolution graphs permit the following conclusions:

- Decreased consumption of SU did not translate in proportional decrease in the correspondent expenditure, suggesting stabilization between branded and generic marketed sulfonylureas during the analysed period;
- Marked increase in consumption of biguanides was not proportional to the increase in the correspondent expenditure, suggesting merging of generic drugs during the analysed period;
- Variable consumption patterns of the antidiabetic market are driven by cost-effectiveness relationship and thus are mainly due to the balance between introduction of new therapeutic options and merging of generic drugs, which translate the evolution of intellectual development and interpretation of the disease.

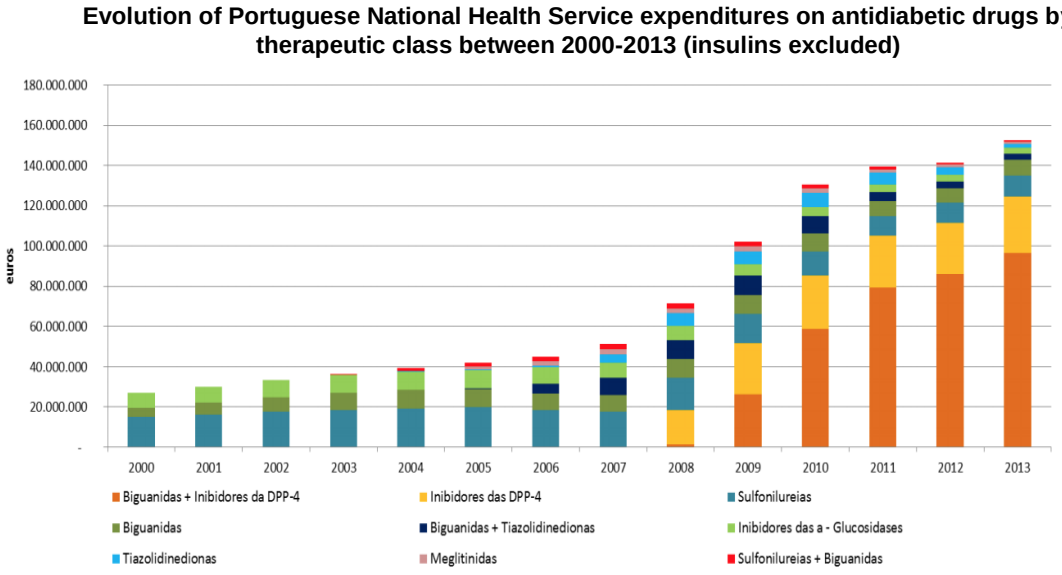


Figure 5 – Graphic representation of Portuguese National Health Service expenditure on antidiabetic drugs by therapeutic class between 2000-2013 (insulins excluded). (Adapted from *"Consumo de antidiabéticos 2000-2013", by C. Furtado and R. Oliveira, 2014, p. 5. Copyright by INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde I.P.*)(22)

In this context, NIDDM therapeutic area has been stated as a "crowded market", displaying many branded and generic options, with a sustainable growth expected ahead, referring the 2014 reviewed diabetes pipeline to 198 new medicines to treat either type 1 and type 2 DM, counting 146 drugs with direct application in DM (30 for type 1 DM, 100 for NIDDM and 16 for unspecified diabetes) and 52 drugs for diabetes-related conditions.(25) Suffice it to say that current therapeutic options are considered insufficient therapies since considerably high unmet needs continue to exist, mainly concerning patient awareness and compliance, diagnosis rate, and sustainable efficacy and safety of drugs.(23,26) Despite the well-populated pipeline, several studies reveal that during the next ten years none of the drugs slated to reach the market will significantly diminish the level of unmet needs and new therapeutic classes are not likely to emerge. In order to offset the impact of approaching patent expiries of blockbuster antidiabetic drugs, pharmaceutical companies are prioritizing competitive pricing rather than therapeutic value, returning in the observed saturation of the late-stage pipeline with "me-too" drugs (i.e. drugs that exhibit minor differences compared to those already in the market) and new combinations of existing therapies.(26–30)

However, due to the increasing prevalence and progressive nature of the disease, changes in the current NIDDM therapeutic universe are paramount. In the present scenario where the consumption of add-on therapies is overlapping the SOC segment, with a DDP-4 inhibitor drug (sitagliptin, Januvia®) dominating the non-insulin market, guidelines changes concerning the therapeutic class application are expected for the foreseeable future. A Frost & Sullivan's recent analysis forecasts that DDP-4 inhibitor drugs will continue to dominate the non-insulin market both as single therapy and as fixed-dose combinations with metformin, and that the new SGLT2 class will overtake the GLP-1 class for the number two spot among add-on therapies. As for the said "old therapeutic classes" – biguanides and SU – two options are in stake: change and adapt or eventually fall into disuse (like TZD). For the current first-line therapy metformin, its cost-effectiveness-safety relationship

profile reinforced with new improved formulations already in pipeline phase II (by Elcelyx Therapeutics™), odds tend to confirm its continuity as prime therapy. Concerning SU, statistics speculate a long-term fall into disuse in the NIDDM therapeutic landscape.(20)

This work focus on the application of new synthetic and crystal engineering approaches made over two drugs of the SU therapeutic class of compounds, seeking their reassurance as valid NIDDM therapeutic options with capacity to adapt to the presented market demands.

# Annex 2

## Glibenclamide and gliclazide pharmacodynamics and pharmacokinetics

GBL is rapidly absorbed from the gastrointestinal tract, reaching onset of action and maximum plasma concentration ($C_{max}$), respectively, within 1 hour and 2-4 hours after oral administration. It's absorption rate from stomach, duodenum and colon is practically the same and retention time is greater in the colon. This drug is primarily metabolized in the liver, originating two metabolites through cytochrome P450 glycosylation: 4-*trans*-hydroxyglyburide and 3-*cis*-hydroxyglyburide. These weakly active metabolites do not contribute with clinical significance to GBL hypoglycemic action in humans, being equally excreted through bile and urine (50% by each route), with a clearance of 78 mL/h/Kg. Differently from other sulfonylureas, GBL is characterized for being primarily excreted via urinary tract, fact responsible for marked variations on the clearance parameter of individuals with renal impairment.(31,32) For that, although 4-*trans*-hydroxyglyburide is reported as a non-active metabolite, its retention in the kidneys determine extended hypoglycemic effect (~24h), which can be severe with patients with chronic kidney disease.(33,34) Described as a weak acid, GBL unchanged drug is ~99% nonionically bound to serum proteins, the same occurring to its 4-*trans*-hydroxy derivative (~97%).(35) This high plasma protein binding rate associated to its poor water-solubility lead GBL to determine increased pharmacokinetics and pharmacodynamics variability and bioavailability problems.(36) Consequently, GBL demonstrates a higher hypoglycemic risk profile when compared to other sulfonylureas (~2%), but it is also considered twice as potent as the second-generation agent glipizide.(37) Besides its inadequacy for diabetes treatment in urinary tract impairment patients, for those with associated cardiovascular pathology GBL is considered safer than all other oral anti-diabetic medication, reporting less mortality and morbidity hospital events. In this scope, it has also been proved that GBL decreases the need for photocoagulation and demonstrates a protective effect on the combined microvascular outcomes of retinopathy and nephropathy, two very common diabetes mellitus complications.(37)

Comparatively to GBL, GCZ reaches maximum plasma concentrations approximately four-times higher in one-third of the time past oral administration(38), it also has wider inter- and intra-individual variability.(39) Also, divergently from GBL, GCZ mechanism of action is specific for pancreatic SUR1 receptors (being described as the most selective SU), thus hypoglycaemic adverse events are less common and GCZ are considered safer than GBL. As for GBL, GCZ is also absorbed along gastrointestinal tract, mainly in jejunum (55.9%) and ileum (20.7%), but with a one hundred-times greater mean absorption rate and approximately two-times greater mean retention time. PPB is also marked for this SU, but sufficiently lower to impact a greater distribution volume and, in some cases, a greater half-life. GCZ excretion is mainly processed via renal route (60-70%) with a clearance of 0.78L.h-1, which in turn is considerably lower than GBL's. Although with similar pharmacological efficacy, as a results of its safer profile, GCZ is much more prescribed than GBL.(40) Table 4 resumes GBL and GCZ's pharmacokinetic parameters.

Table 4 – GBL and GCZ pharmacokinetic parameters: Absorption, Distribution, Metabolism and Excretion

| API | ABSORPTION | | | DRISTIBUTION | | | METABOLISM | | EXCRETION | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Local | $t_{max}$ (h) | $C_{max}$ (μg/mL) | PPB | Vd (L) | $t_{1/2}$ (h) | Local | Type | Type | CL ($L.h^{-1}$) | $k_e$ ($h^{-1}$) |
| Glibenclamide | Stomach (AR=0.477±0.133μg.h.mL$^{-1}$; RT=2.67±0.35h) Duodenum (AR=0.475±0.142 μg.h.mL$^{-1}$; RT=2.42±0.48h) Colon (AR=0.486±0.301μg.h.mL$^{-1}$; RT=3.55±0.68h)(41)[1] | 3.03 ±0.23(42)[2] | 0.273 ± 0.0258(42)† | 99% (97% major metabolite)(43) | 9-10(44) | 10(44) | Liver | Hydroxylation by CYP3A4(45) | Renal (50%) Biliary (50%)(43) | 3.1(46)[3] | 0.07(46)‡ |
| Gliclazide | Duodenum (14%) Jejunum (55.9%) Ileum (20.7%) Colon (9.4%)(47)[4] [MAR=32.87±10.32μg.h.mL$^{-1;}$ MRT=6.93±1.87h](38)[5] | 1.64 ±0.49(38)** | 4.20 ±1.33(38)** | 94%(39) | 13-24(39) | 8.1-20.5(39) | Liver | Hydroxylation by CYP2C9(39) | Renal (60-70%) Biliary (10-20%)(48) | 0.78(39) | 0.20 ±0.006(38)** |

**Table Acronyms and Abbreviations:**
AR – Absorption Rate; MAR – Mean Absorption Rate; RT – Retention Time; MRT – Mean Retention Time; $C_{max}$ – Maximum/Peak Plasma Concentration; $t_{max}$ – Time (past administration) at which $C_{max}$ is observed; PPB – Plasma Protein Binding rate; Vd – Distribution Volume; $t_{1/2}$ – Plasma Half-life Time; CL – Clearance (volume of blood cleared of drug per unit time); $k_e$ – Elimination Constant

[1] Randomized crossover study with eight healthy volunteers and six diabetic patients: dosage instilled once into the stomach and once into the duodenum.
[2] Randomized crossover study with twenty-four healthy subjects: administration of 10mg of GBL (two tablets of Daonil 5mg)
[3] Non-obese patients group (n=8): maximum dosage of 20mg per day, 12 weeks of tratment.
[4] *In-vivo* observed data after oral administration of 80 mg of GCZ (immediate release tablets).
[5] *In-vivo* observed data after oral administration of modified release minitablets in rats.

## Attachments References


1. American Diabetes Association AD. Diagnosis and classification of diabetes mellitus. Diabetes Care [Internet]. American Diabetes Association; 2010 Jan [cited 2016 Oct 4];33 Suppl 1(Suppl 1):S62-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20042775

2. WHO | About diabetes. WHO. World Health Organization; 2014;

3. Harvard Health Publications. Type 2 Diabetes Mellitus Guide: Causes, Symptoms and Treatment Options [Internet]. Available from: https://www.drugs.com/health-guide/type-2-diabetes-mellitus.html

4. Kumar A, Bharti SK, Kumar A. Type 2 Diabetes Mellitus: The Concerned Complications and Target Organs. Apollo Med. 2014;11(3):161–6.

5. Shulman GI. Cellular mechanisms of insulin resistance. J Clin Invest [Internet]. 2000 Jul [cited 2016 Oct 3];106(2):171–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10903330

6. Morino K, Petersen KF, Shulman GI. Molecular Mechanisms of Insulin Resistance in Humans and Their Potential Links With Mitochondrial Dysfunction. Diabetes. 2006;55(Supplement 2).

7. Tabish SA. Is Diabetes Becoming the Biggest Epidemic of the Twenty-first Century? Int J Health Sci (Qassim) [Internet]. Qassim University; 2007 Jul [cited 2016 Oct 3];1(2):V–VIII. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21475425

8. World Health Organization (WHO). Global Report on Diabetes. Publ World Heal Organ [Internet]. 2016 [cited 2016 Oct 4]; Available from: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1

9. International Diabetes Federation. IDF Diabetes Atlas 2015. IDF Diabetes Atlas Seventh Ed 2015 [Internet]. 2015 [cited 2016 Oct 4]; Available from: http://www.idf.org/sites/default/files/Atlas7e-poster.pdf

10. IMS Institute for Healthcare Informatics. The Global Use of Medicines: Outlook Through 2015. Glob Use Med Outlook Through 2015 [Internet]. 2011 [cited 2016 Oct 4]; Available from: http://www.imshealth.com:90/files/web/IMSH Institute/Reports/The Global Use of Medicines 2015/Global_Use_of_Medicines_Report2015.pdf

11. Statistica - The Statistics Portal. Global pharmaceutical market revenue 2008-2015 | Statistic [Internet]. Pharmaceutical Products & Market. 2016. Available from: https://www.statista.com/statistics/266039/global-pharmaceutical-market-revenues/

12. Statistica - The Statistics Portal. Antidiabetics drugs revenue worldwide 2008-2015 | Statistic [Internet]. Pharmaceutical Products & Market. 2016. Available from: https://www.statista.com/statistics/312220/anti-diabetics-revenue-worldwide/

13. MedMarket Diligence L. Diabetes management trends – advanced medical technologies [Internet]. WordPress. 2011. Available from: http://blog.mediligence.com/2011/05/26/diabetes-management-trends/

14. Grand View Research. Antidiabetics Market Analysis By Product (Insulin, Biguanides, Thiazolodinediones, GLP-agonists, Sulphonylureas, DPP-4 inhibitors, SGLT-2, Alpha-glucosidase Inhibitors, Meglitinides) and Segment Forecast to 2020

[Internet]. 2015. Available from: http://www.grandviewresearch.com/industry-analysis/antidiabetics-market

15. Reportlinker.com. Therapy Industry Statistics, Market Research & Statistics [Internet]. What Are the Most Profitable Therapies? Market Trends & Strategies Explained. 2016. Available from: http://www.reportlinker.com/ci02266/Therapy.html

16. Colagiuri S. Clinical Guidelines Task Force Global Guideline for Type 2 Diabetes Correspondence, and related literature from IDF Acknowledgements, and sponsors' duality of interest.

17. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA. AACE/ACE Consensus Statement CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM – 2016 EXECUTIVE SUMMARY. 84 Endocr Pract. 2016;22(1).

18. Grunberger G, Handelsman Y, Hirsch IB, Jellinger PS, Mcgill JB, Mechanick JI, et al. AACE/ACE Comprehensive Diabetes Management Algorithm. Endocr Pract. 2015;21(4).

19. Consumer Reports Best Buy Drugs. The Oral Diabetes Drugs: Treating Type 2 Diabetes - Comparing Effectiveness, Safety and Price). 2009 [cited 2016 Oct 11];1–29. Available from: https://www.consumerreports.org/health/resources/pdf/best-buy-drugs/DiabetesUpdate-FINAL-Feb09.pdf

20. Toscano D. MARKET BRIEF - The Market for Type 2 Diabetes Therapeutics - Key Findings From a Recent Analysis of Global Drug Development Efforts | Articles | drug development and delivery back issues | Drug Development & Delivery [Internet]. Drug Development & Delivery. 2013. Available from: http://www.specialtypharma.com/Main/Back-Issues/MARKET-BRIEF-The-Market-for-Type-2-Diabetes-Therap-641.aspx

21. Abdessadek M, Attari A El, Diarra M, Magoul R, Ouezzani S El, Khabbal Y, et al. CONSUMPTION ANALYSIS OF METFORMIN, SULFONYLUREAS, AND OTHER ANTIDIABETICS DRUGS IN MOROCCO (1991-2005). Int J Pharm Pharm Sci. 2016;8(8):85–8.

22. Furtado C, Oliveira R. Uma análise ao consumo e diferenças entre práticas médicas ao nível nacional e internacional. Consum Antidiabéticos 2000-2013. 2014;

23. GlobalData - PharmaPoint. TYPE 2 DIABETES - GLOBAL DRUG FORECAST AND MARKET ANALYSIS TO 2022 – EVENT-DRIVEN UPDATE. 2014 [cited 2016 Oct 10]; Available from: http://www.marketresearch.com/product/sample-8083520.pdf

24. Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of antidiabetic drugs in the U.S., 2003-2012. Diabetes Care [Internet]. 2014 [cited 2016 Oct 10];37(5):1367–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24623020

25. America's Biopharmaceutical Research Companies. Biopharmaceutical Research Companies Are Developing 180 Medicines to Treat Diabetes and Related Conditions. Med Dev Diabetes [Internet]. 2014 [cited 2016 Oct 14];1–24. Available from: http://www.phrma.org/sites/default/files/pdf/diabetes2014.pdf

26. Gohil K, Enhoffer D. Diabetes market grows ever more crowded. P T [Internet]. MediMedia, USA; 2014 Dec [cited 2016 Oct 14];39(12):877–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25516698

27. Gburcik V. Treating type 2 diabetes – a 21st century pandemic [Internet]. pharmaceutical-technology.com. 2013. Available from: http://www.pharmaceutical-technology.com/features/feature-treating-type-two-diabetes-century-pandemic/

28. Gburcik V. End of the diabetes blockbuster: We are entering the “me-too” era [Internet]. MedCity NewsMedCity News. 2013. Available from: http://medcitynews.com/2013/05/end-of-the-diabetes-blockbuster-we-are-entering-the-me-too-era/?rf=1

29. Drug Development & Delivery. Major Players in Type 2 Diabetes Shifting Focus to Pricing to Maintain Market Share [Internet]. PharmaPoint: Type 2 Diabetes – Global Drug Forecast and Market Analysis to 2025. 2016. Available from: http://drug-dev.com/Main/Back-Issues/Major-Players-in-Type-2-Diabetes-Shifting-Focus-to-1154.aspx

30. Walker T. Diabetes drug spending on the rise. Manag Healthc Exec. 2016;

31. Glyburide Tablets - FDA prescribing information, side effects and uses [Internet]. Available from: https://www.drugs.com/pro/glyburide-tablets.html

32. Donahue SR, Turner KC, Patel S. Pharmacokinetics and Pharmacodynamics of Glyburide/Metformin Tablets (Glucovance???) versus Equivalent Doses of Glyburide and Metformin in Patients with Type 2 Diabetes. Clin Pharmacokinet [Internet]. Springer International Publishing; 2002 [cited 2016 Sep 29];41(15):1301–9. Available from: http://link.springer.com/10.2165/00003088-200241150-00004

33. Ioannidis I. Diabetes treatment in patients with renal disease: Is the landscape clear enough? World J Diabetes [Internet]. Baishideng Publishing Group Inc; 2014 Oct 15 [cited 2016 Sep 29];5(5):651–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25317242

34. Alsahli M, Gerich JE. Hypoglycemia in Patients with Diabetes and Renal Disease. J Clin Med [Internet]. 2015;4:948–64. Available from: www.mdpi.com/journal/jcm

35. Olsen KM, Kearns GL, Kemp SF. Glyburide Protein Binding and the Effect of Albumin Glycation in Children, Young Adults, and Older Adults with Diabetes. J Clin Pharmacol [Internet]. Blackwell Publishing Ltd; 1995 Jul [cited 2016 Sep 29];35(7):739–45. Available from: http://doi.wiley.com/10.1002/j.1552-4604.1995.tb04115.x

36. Smith DA, Di L, Kerns EH. The effect of plasma protein binding on in vivo efficacy: misconceptions in drug discovery. Nat Rev Drug Discov [Internet]. Nature Publishing Group; 2010 Dec [cited 2016 Sep 29];9(12):929–39. Available from: http://www.nature.com/doifinder/10.1038/nrd3287

37. Bolen S, Wilson L, Vassy J, Feldman L, Yeh J, Marinopoulos S, et al. Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes. Agency Healthc Res Qual [Internet]. 2007 [cited 2016 Sep 29];8. Available from: http://www.effectivehealthcare.ahrq.gov/repFiles/OralFullReport.pdf

38. Resztak M, Hermann T, Sawicki W, Danielak D. Pharmacokinetics and pharmacodynamics of gliclazide from immediate and modified release formulation tablets in rats. Iran J Pharm Res IJPR [Internet]. Shahid Beheshti University of Medical Sciences; 2014 [cited 2016 Oct 4];13(1):29–37. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24734054

39. Sarkar A, Tiwari A, Bhasin PS, Mitra M. Pharmacological and Pharmaceutical Profile of Gliclazide: A Review. J Appl Pharm Sci [Internet]. 2011 [cited 2016 Oct 4];1(9):11–9. Available from: http://www.japsonline.com/admin/php/uploads/253_pdf.pdf

40. Singh AK, Singh R. Is gliclazide a sulfonylurea with difference? A review in 2016. Expert Rev Clin Pharmacol [Internet]. 2016 Jun 2 [cited 2017 May 21];9(6):839–51. Available from: http://www.tandfonline.com/doi/full/10.1586/17512433.2016.1159512

41. Brockmeier D, Grigoleit HG, Leonhardt H. Absorption of glibenclamide from different sites of the gastro-intestinal tract. Eur J Clin Pharmacol [Internet]. 1985 [cited 2016 Oct 4];29(2):193–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3935463

42. Flores-Murrieta FJ, Carrasco-Portugal Mdel C, Reyes-GarcÌa G, Medina-Santill·n R, Herrera JE. Bioequivalence of two oral formulations of glyburide (glibenclamide) [Internet]. Proceedings of the Western Pharmacology Society. 2007 [cited 2016 Sep 29]. p. 64–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18605232

43. Canadian Institutes of Health Research, Alberta Innovates (HealthSolutions), The Metabolomics Innovation Centre (TMIC). DrugBank: Glyburide [Internet]. OMx Personal Health Analytics, Inc. 2005 [cited 2016 Sep 28]. Available from: http://www.drugbank.ca/drugs/DB01016

44. Chahal H. Comparative Safety and Efficacy of Glibenclamide in the Elderly. 19th Expert Comm Sel Use Essent Med [Internet]. 2013 [cited 2016 Oct 4];(EML Section 18.5 – Insulin and other medicines used for diabetes). Available from: http://www.who.int/selection_medicines/committees/expert/19/applications/Sulfonylurea_18_5_A_R.pdf?ua=1

45. Zhou X, Rougée LRA, Bedwell DW, Cramer JW, Mohutsky MA, Calvert NA, et al. Difference in the Pharmacokinetics and Hepatic Metabolism of Antidiabetic Drugs in Zucker Diabetic Fatty and Sprague-Dawley Rats. Drug Metab Dispos [Internet]. 2016 Aug [cited 2016 Oct 4];44(8):1184–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27217490

46. Jaber LA, Antal EJ, Slaughter RL, Welshman IR. The pharmacokinetics and pharmacodynamics of 12 weeks of glyburide therapy in obese diabetics. Eur J Clin Pharmacol [Internet]. 1993 [cited 2016 Oct 4];45(5):459–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8112376

47. Grbic S, Parojcic J, Ibric S, Djuric Z. In vitro-in vivo correlation for gliclazide immediate-release tablets based on mechanistic absorption simulation. AAPS PharmSciTech [Internet]. Springer; 2011 Mar [cited 2016 Oct 4];12(1):165–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21181508

48. Research CI of H, Alberta Innovates (HealthSolutions), The Metabolomics Innovation Centre (TMIC). DrugBank: Gliclazide [Internet]. Available from: http://www.drugbank.ca/drugs/DB01120